Stereotactic body radiotherapy for stage I NSCLC: The challenge of evidence-based medicine

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A Moment of Equipoise with Stereotactic Body Radiotherapy

To the Editor:

I am writing with regard to Guckenberger et al.'s[1] article relating the safety and efficacy of stereotactic body radiotherapy (SBR) for stage 1 non–small-cell lung cancer in routine clinical practice.

I agree this is an important therapy that requires continual review to elucidate optimal therapeutic delivery for efficacy and safety concerns and am encouraged by the consistency reported by other studies of the overall 3-year survival of 48% patients.[2]

There is temptation to compare SBR with surgery in the potentially fit patient. A recent review of the U.K. experience in surgical resection of lung cancer by Powell et al.[3] may provide a robust comparison of the safety of the surgical alternative which in no cohort, other than racial, achieved a safety equivalent to SBR. The cohort of stage 1A NSCLC patients had 30- and 90-day mortality rate at 1.6% and 3.4%, respectively. This is significantly worse than SBR, despite being an intrinsically fitter population by virtue of being offered surgery. Is it time to usurp the surgeon?

Overall survival is the last remaining issue to determine whether SBR has a broader role. Alexander et al.[4] have attempted to compare SABR with surgery in elderly patients, however, their study was limited by a lack of age matching of the cohort and the use of sublobar resections. An important, age-matched retrospective review by Varlotto et al.[5] suggests little difference in efficacy of surgery or SBR.

With the technical insights garnered from Guckenberger et al.'s review[1] we are at clinical equipoise and await results of current, prospective randomized trials free of selection bias. In the interim, which is likely to be prolonged, a frank and open discussion of the options with patients is required. At the very least, the former apathy toward management of elderly patients with early-stage lung cancer must be revoked in light of a safe, efficacious, and low-burden therapy such as SBR seems to be.

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REFERENCES

1. Guckenberger M, Allgäuer M, Appold S, et al. Safety and efficacy of stereotactic body radiotherapy for stage i non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. *J Thorac Oncol* 2013;8: 1050–1058.
2. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–1076.
3. Powell HA, Tata LJ, Baldwin DR, Stanley RA, Khakwani A, Hubbard RB. Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit. *Thorax* 2013;68:826–834.
4. Alexander ES, Machan JT, Ng T, Breen LD, DiPetrillo TA, Dupuy DE. Cost and effectiveness of radiofrequency ablation versus limited surgical resection for stage I non-small-cell lung cancer in elderly patients: is less more? *J Vasc Interv Radiol* 2013;24:476–482.
5. Varlotto J, Fakiris A, Flickinger J, Medford-Davis L, Liss A, Shelkey J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non–small cell lung cancer treated with resection or stereotactic radiosurgery. *Cancer*. 2013.

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Stereotactic Body Radiotherapy for Stage I NSCLC

The Challenge of Evidence-Based Medicine

In Response:

We thank Dr. Barlett for his encouraging comment on our article.[1] In the current European Society for Medical Oncology (ESMO)[2] and National Comprehensive Cancer Network (NCCN) V 2.2013 guidelines, stereotactic body radiotherapy (SBRT) is the recommended standard of care for patients with stage I non–small-cell lung cancer, who are inoperable because of medical comorbidities. Robust outcome in a multi-institutional environment despite variability in technical details of planning and delivery is a prerequisite for safe and effective guideline-compliant SBRT practice on a population-based level. Our results therefore support two population-based analyses, which reported an improvement in overall survival for stage I non–small-cell lung cancer in the elderly patient population by the implementation of SBRT,[3,4] providing high level of evidence.

Lobectomy is the accepted standard of care for operable patients. The achievements of high local tumor control and favorable overall survival in a prognostic unfavorable patient population resulted in a transfer of SBRT practice to fitter, healthier patients, who refused surgical resection. Retrospective studies described outcome approaching surgical results, indicating that overall survival after SBRT is mainly compromised by age and comorbidities of the patients and not by inferior oncological efficacy compared with surgical resection.[5,6] On the basis of these

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experiences, three randomized-controlled trials (ROSEL, STAR, RTOG 1021) have been started, all comparing SBRT with surgery, either lobectomy or sublobar resection. However, all three trials closed early because of very poor accrual of patients. Was all the effort of these randomized trials for nothing? Certainly no! From a technical perspective, these trials achieved highly valuable standardization, quality-assurance, and credentialing procedures for implementation and practice of SBRT.[7,8] From a clinical perspective, these trials engaged multidisciplinary discussion and interaction aiming at the best treatment approach for each individual patient.

Propensity-score matching is a statistical tool, which attempts to account for confounding covariates and thereby simulates a randomized trial based on retrospectively acquired data. Several such comparisons have been performed and all concluded that SBRT is at least as effective as sublobar resection and comparable with lobectomy.[4,9–11] This conclusion seems robust with reproducible results in these different studies. Nevertheless, only known and available confounding covariates were statistically corrected, which leaves uncertainties behind.

How to proceed now that level-one evidence will not be available for comparison of SBRT and surgical resection? In daily clinical practice, patients should not only be discussed but be informed by a multidisciplinary team about the available (or lack of) evidence, the surgical and SBRT options, and their specific pros and cons. This is especially true for the elderly and comorbid patient population as stated by Dr. Barlett but the encouraging outcome of SBRT might increase the number of younger and fitter patients actively refusing surgery and opting for SBRT: we should prepare ourselves with the establishment of prospective databases for future generation of the highest data quality and evidence possible in the absence of randomized trials.

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REFERENCES

1. Guckenberger M, Allgäuer M, Appold S, et al. Safety and efficacy of stereotactic body radiotherapy for stage i non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. *J Thorac Oncol* 2013;8:1050–1058.
2. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al.; ESMO Guidelines Working Group. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi89–vi98.
3. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;28:5153–5159.
4. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012;84:1060–1070.
5. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352–1358.
6. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;83:348–353.
7. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. *Radiat Oncol* 2009;4:1.
8. Hurkmans CW, van Lieshout M, Schuring D, et al. Quality assurance of 4D-CT scan techniques in multicenter phase III trial of surgery versus stereotactic radiotherapy (radiosurgery or surgery for operable early stage (stage 1A) non-small-cell lung cancer [ROSEL] study). *Int J Radiat Oncol Biol Phys* 2011;80:918–927.
9. Varlotto J, Fakiris A, Flickinger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. *Cancer* 2013;119:2683–2691.
10. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. *Ann Oncol* 2013;24:1543–1548.
11. Puri V, Crabtree TD, Kymes S, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. *J Thorac Cardiovasc Surg* 2012;143:428–436.

ALK FISH in Non–Small-Cell Carcinomas of the Lung

What about False-Positive Results?

To the Editor:

In their report, Sholl et al.[1] elegantly demonstrate strong association between anaplastic lymphoma kinase immunohistochemistry (ALK IHC) and *ALK* fluorescence in situ hybridization (FISH) for detecting ALK rearrangements in lung adenocarcinoma. Using the clone 5A4 the authors observed that ALK IHC was 93% sensitive and 100% specific when compared with *ALK* FISH. We agree with their conclusion that a combined FISH and IHC approach enhances chances to identify ALK rearrangements in non–small-cell lung cancer.

However, we would like to comment on their interpretation of a FISH result considered as false positive.

In case 2, *ALK* FISH reveals tumor nuclei showing multiple fused signals (>2) associated with a single green signal (Fig. 2).[1] The authors interpret this profile as an atypical *ALK* rearrangement, arguing for an asymmetric splitting of the green probe (5′ centromeric) consisting of a single bright-green signal in addition to a small green signal fused to a red signal.

But the *ALK* breakpoint is known to be constant.[2] This molecular feature justifies the use of the Vysis ALK Break Apart FISH Probe Kit with a green probe (5' centromeric) and a red probe (3′ telomeric, complementary to the *ALK* tyrosine kinase domain) surrounding the *ALK* breakpoint. *ALK* rearrangement leads to an increased distance between the green signal (5′) and the red signal (3′). Single red signals (3′), without corresponding green signals, because of a deletion of 5′ end of *ALK*,

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